42. Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP Jr. Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol 1985:44;559–577.
43. Levivier M, Gash DM, Przedborski S. Time course of the neuroprotective effect of transplantation on quinolinic acid-induced lesions of the striatum. Neuroscience 1995;69:43–50.
44. Martinez-Serrano A, Bjorklund A. Protection of the neostriatum against excitotoxic damage by neurotrophin-producing, genetically modified neural stem cells. J Neurosci 1996;16:4604–4616.
45. Kordower JH, Isacson O, Emerich DF. Cellular delivery of trophic factors for the treatment of Huntington's disease: is neuroprotection possible? Exp Neurol 1999;159:4–20.

CME

# Regional and progressive thinning of the cortical ribbon in Huntington's disease

H.D. Rosas, MD; A.K. Liu, PhD; S. Hersch, MD, PhD; M. Glessner, BA; R.J. Ferrante, PhD; D.H. Salat, PhD; A. van der Kouwe, PhD; B.G. Jenkins, PhD; A.M. Dale, PhD; and B. Fischl, PhD

**Abstract—***Background:* Huntington's disease (HD) is a fatal and progressive neurodegenerative disease that is accompanied by involuntary movements, cognitive dysfunction, and psychiatric symptoms. Although progressive striatal degeneration is known to occur, little is known about how the disease affects the cortex, including which cortical regions are affected, how degeneration proceeds, and the relationship of the cortical degeneration to clinical symptoms. The cortex has been difficult to study in neurodegenerative diseases primarily because of its complex folding patterns and regional variability; however, an understanding of how the cortex is affected by the disease may provide important new insights into it. *Methods:* Novel automated surface reconstruction and high-resolution MR images of 11 patients with HD and 13 age-matched subjects were used to obtain cortical thickness measurements. The same analyses were performed on two postmortem brains to validate these methods. *Results:* Regionally specific heterogeneous thinning of the cortical ribbon was found in subjects with HD. Thinning occurred early, differed among patients in different clinical stages of disease, and appeared to proceed from posterior to anterior cortical regions with disease progression. The sensorimotor region was statistically most affected. Measurements performed on MR images of autopsy brains analyzed similarly were within 0.25 mm of those obtained using traditional neuropathologic methods and were statistically indistinguishable. *Conclusions:* The authors propose that the cortex degenerates early in disease and that regionally selective cortical degeneration may explain the heterogeneity of clinical expression in HD. These measures might provide a sensitive prospective surrogate marker for clinical trials of neuroprotective medications.

NEUROLOGY 2002;58:695–701

Huntington's disease (HD) is a progressive, fatal, autosomal dominant neurodegenerative disease, characterized neuropathologically by the progressive degeneration of the basal ganglia and clinically by abnormalities of movement, cognition, and behavior. Because of the severe pathologic changes that the striatum undergoes, it has often been presumed to be the direct or indirect site of most of the clinical symptoms of HD. It is likely that some of the clinical symptoms of the disease are also related to cortical dysfunction and degeneration. The anatomic interconnectedness between the striatum and cortex makes it difficult to understand how dysfunction or degeneration of the striatum, the cerebral cortex, or both contributes to symptoms of HD. The striatum receives reciprocal topographically organized projections from many cortical regions. Projections from the temporal, parietal, and occipital association areas have been shown to terminate as irregular patches in all divisions of the caudate nucleus,[1] while projections from the premotor,[2] primary motor,[2] and somatosensory[3] regions have been shown to terminate almost exclusively in the putamen.

Pathologic changes in cortical regions of the brain

From the Department of Neurology (Drs. Rosas and Hersch), Massachusetts General Hospital and Harvard Medical School, and Departments of Neurology, Pathology, and Psychiatry (Dr. Ferrante), Boston University School of Medicine; MGH-NMR Center (Drs. Rosas, Liu, Salat, van der Kouwe, Jenkins, Dale, and Fischl, M. Glessner), Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Charlestown; and Geriatric Research Education and Clinical Center (Dr. Ferrante), Bedford VA Medical Center, MA.

Supported by the National Institute of Neurological Disorders and Stroke (NS02060; H.D.R.); NS35255, AT00613, and HDSA Coalition for the Cure (S.H.); National Institute of Neurological Disorders and Stroke, National Institute of Mental Health, and National Cancer Institute (NS39581; B.F. and A.M.D.); NIH-funded grants (NS37102 and NS35255), Department of Defense (AT00613, AG13846, and AG12992), Veterans Administration, and Huntington's Disease Society of America (R.J.F.); and NIH AG05886 (D.H.S.).

Received August 24, 2001. Accepted in final form November 27, 2001.

Address correspondence and reprint requests to Dr. H.D. Rosas, Department of Neurology, Massachusetts General Hospital, MGH East, Bldg. 114, Suite 2000, 114 16th Street, Charlestown, MA 02129-4404; e-mail: rosas@helix.mgh.harvard.edu

 

have long[4] been known to occur in HD, including occipital, parietal, temporal, primary motor, cingulate, and prefrontal cortices, which have been reported to show neuronal loss in postmortem studies.[4-6] However, the precise patterns of cortical degeneration in HD have not been well characterized primarily because accurately measuring the degree of cortical atrophy is technically difficult; it is more difficult to quantify changes in an extensively folded sheet (cortex) than the compact basal ganglia structures.

Little is actually known about the regional specificity and relationship of the cortical degeneration to the clinical symptoms. Several neuropathologic studies have demonstrated generalized cortical atrophy, but these studies were generally performed on postmortem tissue of individuals who died in advanced stages of disease. Only few patients have been examined in early stages of disease. It is not known how the cortex degenerates; that is, if it occurs uniformly or nonuniformly, some areas degenerating earlier or more rapidly than other areas.

Morphometric studies done in vivo, including those of presymptomatic gene-positive individuals, have been generally limited to the determination of brain volumes, suggesting early loss of frontal lobe volumes.[7-9] Pathologic measurements of cortical thickness, however, have been particularly difficult to obtain because the highly folded nature of the cortex can result in measurement errors in regions in which the cortical surface is not perpendicular to any of the cardinal axes. Not only are these types of analyses prone to overestimates, but they may provide only limited information as there is considerable natural heterogeneity in thickness from region to region or even within brain regions. Additionally, it is not technically possible to sample more than a small number of cortical regions from a single brain. What little is known comes from studies on autopsy material that sampled regions of cortex and extrapolated volumes or estimated cortical thickness.[4-6]

We present results from automated surface reconstruction, transformation, and high-resolution intersubject alignment procedures for accurately measuring the thickness of the cerebral cortex across the entire brain as well as for generating cross-subject statistics in a coordinate system based on cortical anatomy[10-12] in a cohort of patients with HD. We performed the same analyses on two postmortem brains and compared the measurements obtained using these techniques with the measurements obtained using classic neuropathologic techniques. We found that the two measurements were statistically indistinguishable. Our results suggest that cortical degeneration is present in early stages of disease and may explain at least some of the clinical symptoms.

**Subjects and methods.** *Subjects.* Subjects with HD were recruited from the Massachusetts General Hospital (MGH) Huntington's Disease Unit. Each subject had definite clinical signs of HD[13] as well as either a positive family history or a known trinucleotide repeat expansion. Procedures were fully explained to all subjects, and written informed consent was obtained before scanning. Scanning was performed in compliance with the relevant laws and institutional guidelines of the Internal Review Board of the MGH. Eleven subjects with HD were scanned: six men and five women. The mean age of HD subjects was 43.8 ± 10.3 years. All subjects, except for one with advanced disease, were living independently at the time of scanning. HD subjects were in various stages of disease, ranging from recent onset of motor symptoms (one; 1 year from onset of motor symptoms) to advanced (one; 10 years from onset of motor symptoms). Thirteen normal age-matched control subjects were scanned: eight men and five women. The mean age of normal subjects was 44.5 ± 9 years. All HD subjects were right-handed; 12 of the normal control subjects were right-handed.

*Imaging.* We utilized a Siemens 1.5 T Signa scanner (Milwaukee, WI) to obtain our scans. T1-weighted images were obtained from subjects; image acquisition included echo time (TE) = 3.0 ms, repetition time (TR) = 7.25 ms, flip angle = 7°, field of view = 256 mm, matrix = 256 × 192, 1.33-mm sagittally acquired slices, number of excitations = 1. High-resolution proton density images of postmortem brains were obtained; image acquisition included TE = 14 ms, TR = 10,000 ms, flip angle = 180°, and slice thickness = 1 mm. Ten proton density scans were acquired for each postmortem brain. Two acquisitions were obtained for each living subject. Scans were motion corrected and averaged.

*Surface reconstructions and estimation of cortical thickness.* In vivo data. MRI data were analyzed and the surfaces reconstructed as described previously.[11,12] In brief, an estimate of the gray/white boundary was constructed by classifying all white matter voxels in an MRI volume. The surface of the connected white matter voxels was refined to obtain subvoxel accuracy in the representation of the gray/white boundary and then subsequently deformed outward to find the pial surface as described previously.[14] The surface deformation involves the local adaptive estimation of the MRI values at the gray/white and pial surfaces. The deformation is accomplished by minimizing a constrained energy functional, with the constraint that the surface be smooth at the spatial scale of a few millimeters. In addition, an absolute constraint is placed on the surface during the deformation, which maintains the natural topology of the brain. Figure 1A demonstrates the cortical models that are generated with our surface reconstruction techniques. The left panel demonstrates a sample brain used to generate the analyses. The right panel demonstrates the inflated surface. Light gray areas correspond to gyri and dark gray areas correspond to sulci. The inflated brain allows for better visualization of sulcal regions while maintaining topology.

Cortical thickness estimates were obtained as follows. For each point on the white matter surface, the shortest distance to the pial surface was first computed. Next, for each point on the pial surface, the shortest distance to the white matter was found, and the cortical thickness at that location was set to the average of these two values. All subjects were aligned to a common surface template using a high-resolution surface-based averaging technique that

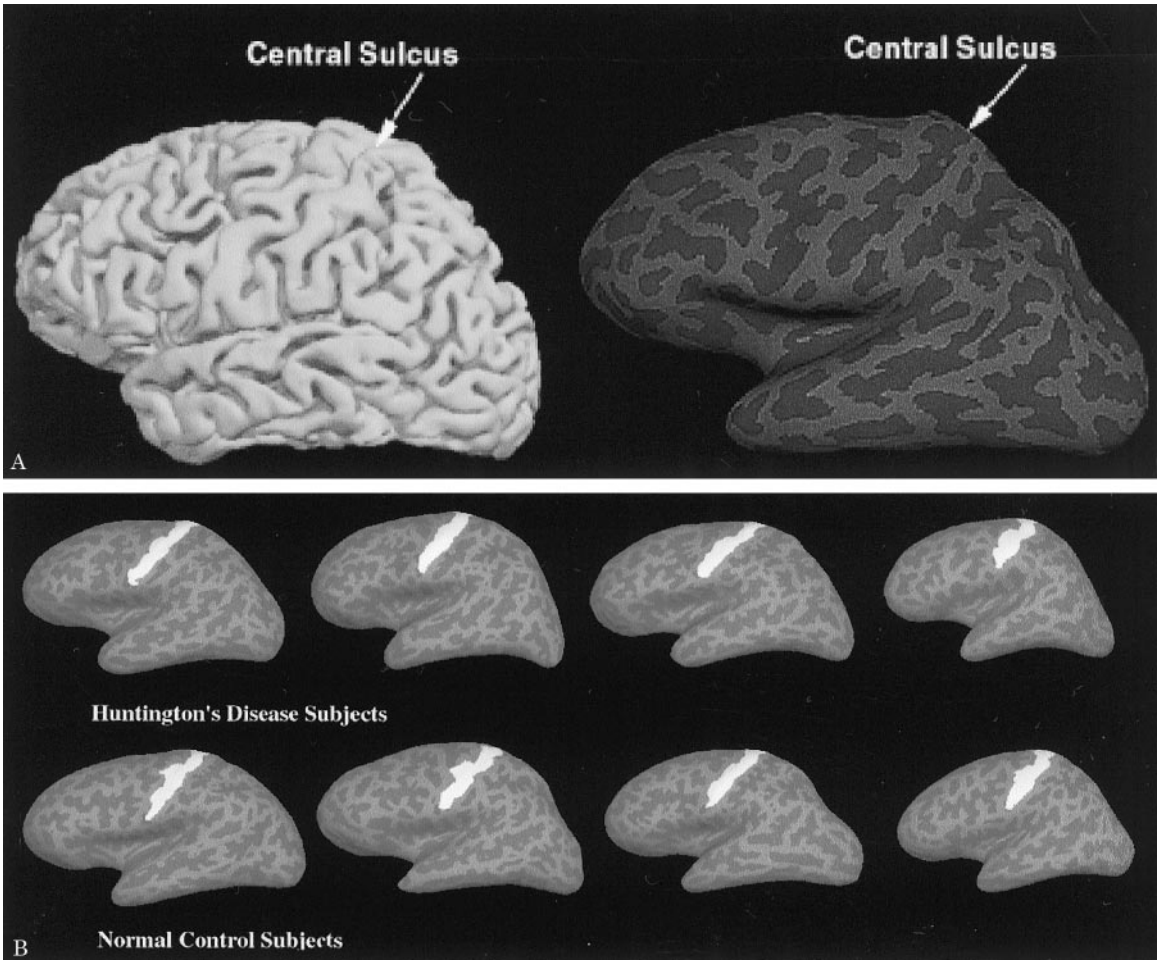


*Figure 1. (A) Surface reconstructions: three-dimensional rendering (left) and inflated brain (right). (B) Mapping of the central sulcus, reverse transformation. The central sulcus was painted onto the common surface template and the transformation reversed back into original surfaces of four subjects with Huntington's disease (top) and four normal control subjects (bottom). The central sulcus aligns correctly in both groups.*

aligns cortical folding patterns.[12] To test whether alignment to the common surface could performed accurately in brains that might be spatially distorted because of atrophy, as may be seen in HD, the central sulcus was painted onto the common surface and the transformation was reversed, transferring the label onto the original surfaces. Figure 1B demonstrates that the central sulcus registers perfectly from the backward registration. A small surface-based Gaussian blurring kernel with an SD of 7 mm was applied to the thickness estimates to remove noise-induced variations in the measurements. Each spatial location was then treated as a random variable, with one observation per subject.

*Statistical analysis.* The statistical maps were generated using a random effects model with 1 degree of freedom for each subject to generate a *t*-test for each cortical location. Thickness maps from the 11 subjects with HD were averaged using our high-resolution surface-based averaging techniques and compared with thickness measurements from the thickness maps of the normal control subjects averaged equivalently. Mean cortical thickness and variance of the mean were calculated at each location.

*Autopsy data.* To validate our measurements, we performed the same analyses on two postmortem brains: one from an individual with HD and one from an age-matched normal control subject. Ten high-resolution three-dimensional proton density scans were obtained from each postmortem brain and averaged off-line. The surface models of the cortex were then constructed (figure 2), and the thickness of the cortex was estimated as described. One-centimeter blocks were then removed from the fixed brains in regions of relatively low curvature near the crowns of gyri, so that accurate manual thickness measurements could be made. Photographs were taken of the exposed surfaces (see figure 2); these were scanned, and the images were used to estimate the thickness of the cortex with NIH Image (Bethesda, MD). Ten measurements were made in each region and then averaged to obtain the mean thickness for each block. The fixed brains were then rescanned, and these MR images were used to locate the precise region of the removed block in the reconstructed cortical model. The automated thickness measures were then sampled and averaged in the corresponding regions.

**Results.** *Cortical thickness measures.* Figure 3A demonstrates absolute cortical thinning measurement using the average folding pattern of the surface reconstructions

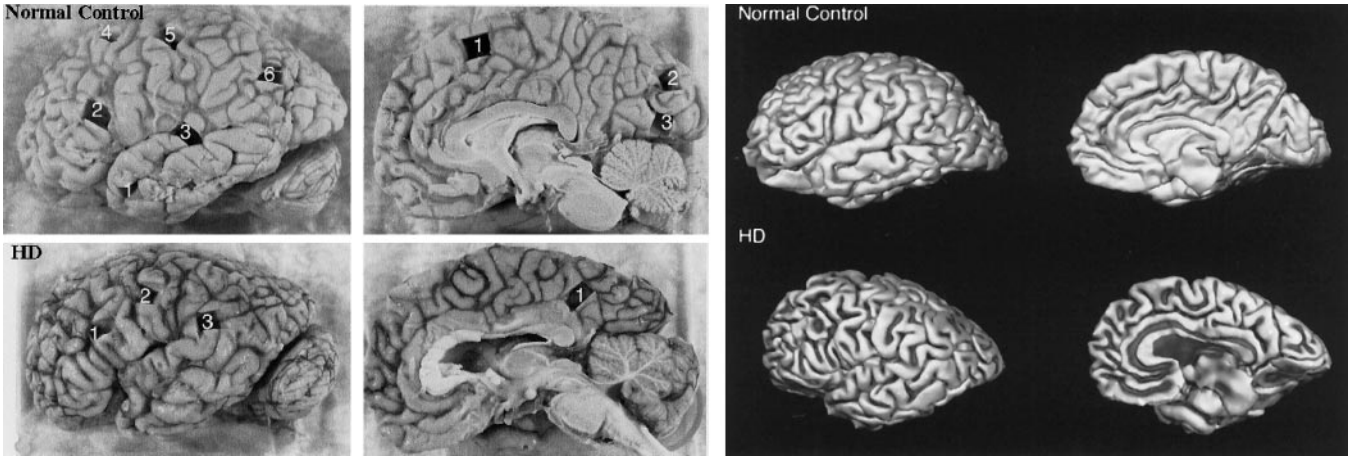


*Figure 2. Surface reconstruction of postmortem brains. (Left) Photographs of postmortem brains. (Right) surface reconstructions obtained from high-resolution scans of the corresponding postmortem brains. (Top panels) Normal control. (Bottom panels) Subject with Huntington's disease. The numbers shown in the photographs correspond to regions from which cortical thickness measurements were made.*

of three separate HD subjects in early, mid, and late clinical stages of disease compared with normal age-appropriate control subjects. The color scale shows the dynamic range of thinning from red to yellow, demonstrating lesser to greater areas of thinning across the Gaussian kernel. Full yellow corresponds to at least 0.4 mm of thinning. The thickness maps demonstrate that cortical thinning occurs in all stages of disease. The greatest differences between the HD and normal control subjects were on the order of 1 mm. Patchy cortical thinning was more prominent in the left hemisphere. In the early case, cortical thinning was most prominent over the middle occipital region, the middle temporal region, and the angular and supramarginal gyri. These areas correspond roughly with Brodmann areas 40, 18, 19, 39, and 44. With increasing duration of illness, thinning extended to more extensively involve the aforementioned areas and to more anterior regions, corresponding roughly to Brodmann areas 18, 19, 44, 3, 2, and 1. In the more advanced case, cortical thinning was more generalized and extended further anteriorly to include most of the frontal lobe; more specifically, this included Brodmann areas 45, 46, 6, 9, and 10. In each case, cortical thinning was more prominent in the left hemisphere.

Figure 3B demonstrates statistical maps comparing the average thickness of all 11 HD subjects in different clinical stages of disease compared with the 13 normal control subjects. Regions of statistically thinner ($p < 0.001$) cortex in HD subjects are color coded, with red to yellow indicating a lesser to greater significance (yellow corresponding to $p < 0.005$). HD subjects had significantly thinner cortical ribbons bilaterally, most prominently in pre- and postcentral regions (Brodmann areas 4, 3, 2, and 1), inferior temporal region (Brodmann 37), and dorsal occipital cortex (Brodmann 17, 18, and 19). Once again, cortical thinning was more prominent over the left hemisphere.

*Validation: Surface reconstruction of brain pathology.* Ten cortical thickness measurements were taken at each location. The average of the 10 measurements obtained using these two methods agreed in all locations to within 0.20 mm (figure 4), with a mean difference of 0.077 mm, confirming the accuracy of the automated technique.

**Discussion.** We report thinning of the cortical gray ribbon in subjects with HD using novel automated surface reconstruction and high-resolution intersubject registration procedures of MR images.[10-12] Thinning was more prominent over more posterior cortical regions earlier in the disease; with increasing duration of symptoms, more anterior cortical regions were affected. Cortical thinning was heterogeneous, even within gyral regions. Some areas were as much as 1 mm thinner. The thickness of the cerebral cortex varies between 1 and 4.5 mm, with an overall thickness of approximately 2.5 mm across the entire brain[15,16]; hence, 0.4 mm of thinning corresponds to approximately a 20% loss of thickness. In some areas, thinning was as much as 1 mm, corresponding to >30% loss of thickness. Our data suggest that the cortex undergoes a gradual, regionally specific, and progressive degeneration, much of which occurs in the striatum.

Our findings, which suggest that more posterior cortical regions degenerate earlier, are provocative. Previous neuropathologic studies have reported early posterior cortical degeneration.[17] In addition, several in vivo reports have also suggested early dysfunction of posterior cortical regions. For example, several neuropsychologic studies have reported early profound impairments in visual recognition, including impaired face and facial expression and facial recognition even relatively early in the disease[18] and recognition of disgust.[19] These are functions thought to be subserved by the temporal lobes; TE, a higher visual area in the temporal lobe, is known to be an output target of the striatum.[20] In another study,[21] patients with HD also showed greater impairment than patients with AD on a test of pattern recogni-

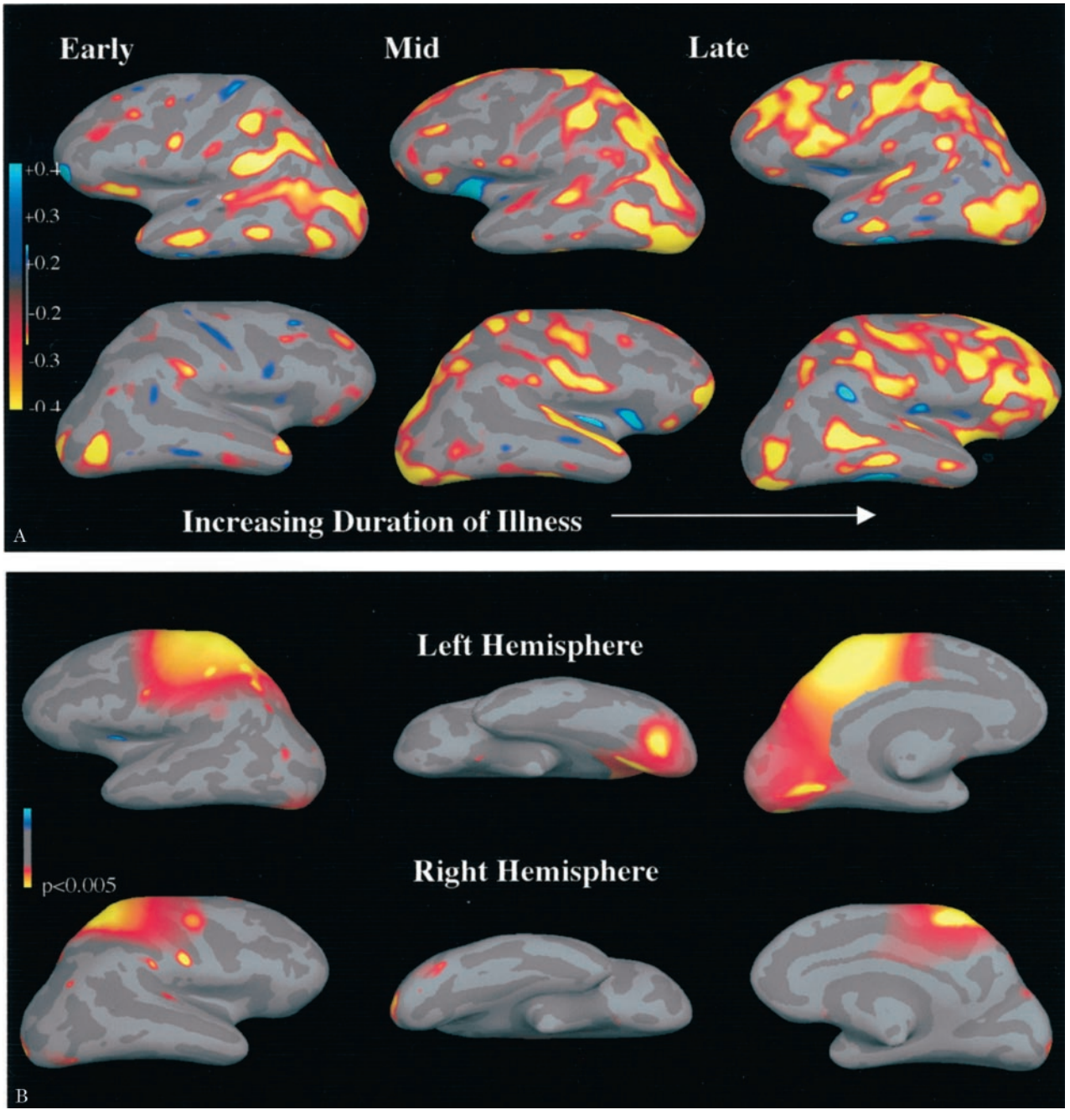


*Figure 3. (A) Mean thickness maps. The surface reconstruction demonstrates mean thickness differences of three different subjects with Huntington's disease (HD) in differing stages of disease. Darker gray areas correspond to sulci; lighter gray areas correspond to gyri. The entire dynamic range of thinning is shown from red to yellow, indicating lesser to greater thinning. Full yellow corresponds to ≥0.4-mm thinning. These maps demonstrate reduction of the thickness of the cortical gray prominently over posterior regions early in disease, which appears to involve more anterior regions and become more generalized as the disease progresses. Left hemispheres are shown on the top, right hemispheres on the bottom. (B) Statistical maps. The average statistical map of 11 subjects with HD was compared with the average map of 13 control subjects. Thinning across subjects was most significant over the sensorimotor regions.*

tion memory, sensitive to temporal lobe lesions and amygdalohippocampectomy but not to frontal lobe lesions. Patients with HD have been shown to demonstrate deficits in spatial working memory, demonstrating a high degree of perseverative responses and difficulties with attentional set shifting, referable to lateral and eventually ventral prefrontal cortical dysfunction.[22] Later involvement of the frontal lobes is supported by work done using MR morphometry, which demonstrated evidence of volume loss of the frontal lobes only in individuals who were moderately affected by disease but not in individuals in early stages of disease.[7] Additionally, frontal lobe volumes did not correlate with symptom severity or general cognitive dysfunction. These observations suggest that cognitive dysfunction may be related to

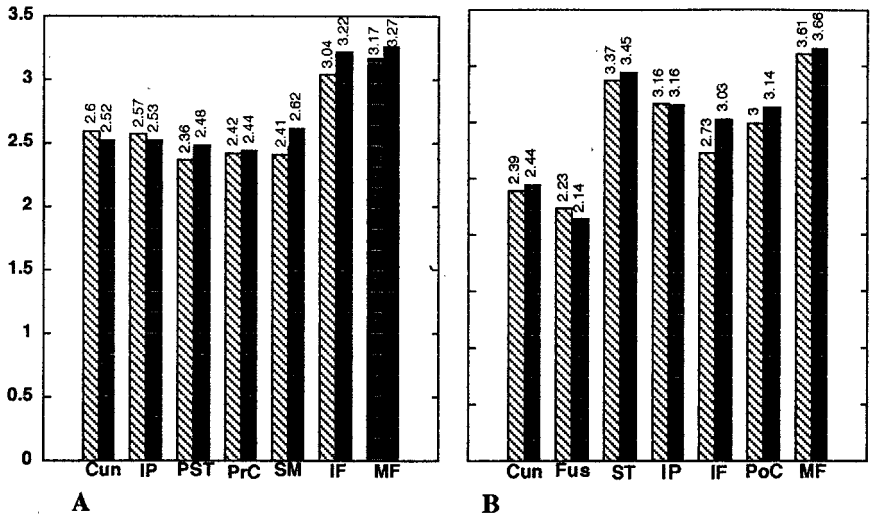


*Figure 4. Postmortem and MR measurement correlations. (A) Measurements obtained from the regions in cortex that were sampled, as demonstrated in figure 2. On the left is normal brain. (B) Measurements obtained from Huntington's disease brain. Hatched columns represent the means of 10 thickness measurements obtained from the pathology sections, using standard neuropathologic methods. Solid bars represent the means of 10 automated thickness measurements obtained using the surface reconstruction techniques. Error bars are not shown as the error was too small to permit error bars. Cun = cuneus; IP = inferior parietal; ST = superior temporal; PrC = precuneus; SM; IF = inferior frontal; MF = middle frontal; Fus = fusiform gyrus; ST = superior temporal; PoC = postcentral.*

disruption or alterations of not only known frontostriatal circuits[23] but also of other less well-characterized circuits involving more posterior cortical regions. A larger study may more fully address the temporospatial patterns of cortical degeneration that occur in HD.

Across all subjects in different stages of disease, we found statistically significant cortical thinning in the sensorimotor region. Thinning of the sensorimotor region has also been reported in previous neuropathologic studies[24] and might be expected based on the known topology of striatal pathology and known corticostriatal connections. In both the mean thickness and the statistical maps, the left hemisphere was more affected. Interestingly, this laterality is consistent with a similar laterality we have previously observed both in striatal atrophy and in lactate elevation in HD,[25] suggesting that the left corticostriatal system may be affected in concert by the disease process.

We performed the same analysis on two postmortem brains to validate our methods. Measurements were taken from crown regions as these regions provided the greatest likelihood of sampling perpendicular to the plane of section. Measurements obtained using these advanced methods on MR images acquired from the postmortem brains and with traditional neuropathologic techniques were within 0.2 mm of each other. This suggests that our novel surface reconstruction methods accurately measure cortical changes that are occurring in the disease.

Thinning of the cortical ribbon has been reported previously in HD in a number of neuropathologic studies.[26-28] Layers III, V, and VI have demonstrated significant loss of pyramidal cells in a study of dorsolateral prefrontal cortex[27] and in another study of dorsal frontal cortex.[28] Morphologic changes occur in striatal medium spiny neurons[29] and in cortical pyramidal cells[30] prior to degeneration, including dendritic remodeling and altered size and number of dendritic spines. This suggests they undergo a period of stress and injury before succumbing, which could be related to the presence of huntingtin aggregates. The dysmorphology and loss of dendrites and axons that occur in this predegenerative period likely cause thinning of the cortical ribbon as well as neuronal loss. Therefore, the site of predilection for neuronal loss in layers III, V, and VI, lamina of origin of corticocortical and corticosubcortical projections, could provide a substrate for the clinical deficits in HD.

The application of these types of analyses to more and better-characterized subjects could provide a better understanding about structure–function relationships between the striatum and the cerebral cortex and how they are altered in HD. This is of special importance as individuals transition from health to illness. This basic understanding not only will provide powerful insight into the disease but may also be a sensitive measure of disease severity and hence a much needed surrogate marker of disease for use in therapeutic clinical trials.


### Acknowledgment

The authors thank Dr. Jean-Paul Vonsattel for encouragement, support, and insightful comments; our research subjects; and the families who generously donated the postmortem material used in the study.


## References


1. Yeterian EH, van Hoesen GW. Corticostriate projections in the rhesus monkey: the organization of certain corticocaudate connections. Brain Res 1978;139:43–63.
2. Kunzle H. Bilateral projections from precentral motor cortex to the putamen and other parts of the basal ganglia. An autoradiographic study in *Macaca fascicularis*. Brain Res 1975;88:195–209.
3. Kunzle H. Projections from the primary somatosensory cortex to basal ganglia and thalamus in the monkey. Exp Brain Res 1977;30:481–492.
4. Halliday GM, McRitchie DA, Macdonald V, et al. Regional specificity of brain atrophy in Huntington's disease. Exp Neurol 1998;154:663–672.

5. De la Monte S, Vonsattel J, Richardson E. Morphometric demonstration of atrophic changes in the cerebral cortex, white matter, and neostriatum in Huntington's disease. J Neuropathol Exp Neurol 1988;47:516–525.
6. Mann DMA, Oliver R, Snowden JS. The topographic distribution of brain atrophy in Huntington's disease and progressive supranuclear palsy. Acta Neuropathol 1993;85:553–559.
7. Aylward E, Anderson N, Bylsma F, et al. Frontal lobe volume in patients with Huntington's disease. Neurology 1998;50: 252–258.
8. Bamford KA, Caine ED, Kido DK, Plassche WM, Shoulson I. Clinical–pathologic correlation in Huntington's disease: a neuropsychological and computed tomography study. Neurology 1989;39:796–801.
9. Harms L, Meierkord H, Timm G, Pfeiffer L, Ludolph A. Decreased *N*-acetyl-aspartate/choline ratio and increased lactate in the frontal lobe of patients with Huntington's disease: a proton magnetic resonance spectroscopy study. J Neurol Neurosurg Psychiatry 1997;62:27–30.
10. Fischl B, Sereno MI, Tootell RBH, Dale AM. High-resolution inter-subject averaging and a coordinate system for the cortical surface. Hum Brain Map 1999;8:272–284.
11. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis II. Inflation, flattening, a surface-based coordinate system. Neuroimage 1999;9:195–207.
12. Dale AM, Fischl B, Sereno M. Cortical surface-based analysis I. Segmentation and surface reconstruction. Neuroimage 1999;9:179–194.
13. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996;11: 1–4.
14. Fischl B, Dale A. Measuring the thickness of the human cerebral cortex. Proc Natl Acad Sci USA 2000;97:11050–11055.
15. von Economo C. The cytoarchitectonics of the human cerebral cortex. London: Oxford University Press, 1929.
16. Brodmann K. Vergleichende Lokalisationslehre der GroBhirnrinde in ihren Pinczipien dargestellt auf Grund des Zellenbaues. Leipzig: Barth, 1909.
17. Lange HW. Quantitative changes of telencephalon, diencephalon, and mesencephalon in Huntington's chorea, postencephalitic, and idiopathic parkinsonism. Verb Anat Ges 1981;75: 923–925.
18. Jacobs DH, Shuren J, Heilman K. Impaired perception of facial identity and facial affect in Huntington's disease. Neurology 1995;45:1217–1218.
19. Sprengelmeyer R. Loss of disgust: perception of faces and emotions in Huntington's disease. Brain 1996;119:1647–1665.
20. Middleton FA, Strick PL. The temporal lobe is a target of output from the basal ganglia. Proc Natl Acad Sci USA 1996; 93:8683–8687.
21. Lange K, Sahakian B, Quinn N, Marsden C, Robbins Y. Comparision of executive and visuospatial memory function in Huntington's disease and dementia of Alzheimer type matched for degree of dementia. J Neurol Neurosurg Psychiatry 1995;58:598–606.
22. Dias R, Robbins TW, Roberts AC. Dissociation in prefrontal cortex of attentional and affective shifts. Nature 1996;380:69–72.
23. Alexander G, Delong M, Strick P. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357–381.
24. Hersch SM, Rosenfeld B, Gutekunst C-A, Rees HD, Green RC. A quantitative laminar analysis of cerebral cortical degeneration in Huntington's disease. Soc Neurosci Abst 1991.
25. Jenkins B, Rosas H, Chen Y, et al. $^{1}$H NMR spectroscopy studies of Huntington's disease: correlations with CAG repeat numbers. Neurology 1998;50:1357–1365.
26. Hedreen J, Peyser C, Folstein S, Ross C. Neuronal loss in layers V and VI of cerebral cortex in Huntington's disease. Neurosci Lett 1991;133:257–261.
27. Sotrel A, Williams RS, Kaufman WE, Myers RH. Evidence for neuronal degeneration and dendritic plasticity in cortical pyramidal neurons in Huntington's disease: a quantitative Golgi study. Neurology 1993;43:2088–2096.
28. Peyser C, Wagster M, Hedreen J, et al. Neuropathology of frontal cerebral cortex in Huntington's disease. Soc Neurosci Abst 1991.
29. Ferrante RJ, Kowall NW, Richardson EP. Proliferative and degenerative changes in striatal spiny neurons in Huntington's disease: a combined study using the section Golgi method and calbindin D28K immunocytochemistry. J Neurosci 1991;11:3877–3887.
30. DiFiglia M, Sapp E, Chase KO, et al. Aggregation of huntingtin in neuronal intranuclear inclusions in dystrophic neurites in brain. Science 1997;277:1990–1993.